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Non-precautionary aspects of toxicology

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Abstract: Empirical studies in toxicology aim at deciphering complex causal relationships, especially in regard to human disease etiologies. Several scientific traditions limit the usefulness of documentation from current toxicological research, in regard to decision-making based on the precautionary principle. Among non-precautionary aspects of toxicology are the focus on simplified model systems and the effects of single hazards, one by one. Thus, less attention is paid to sources of variability and uncertainty, including individual susceptibility, impacts of mixed and variable exposures, susceptible life-stages, and vulnerable communities. In emphasizing the need for confirmatory evidence, toxicology tends to penalize false positives more than false negatives. An important source of uncertainty is measurement error that results in misclassification, especially in regard to exposure assessment. Standard statistical analysis assumes that the exposure is measured without error, and imprecisions will usually result in an underestimation of the dose-effect relationship. In testing whether an effect could be considered a possible result of natural variability, a 5% limit for “statistical significance” is usually applied,

even though it may rule out many findings of causal associations, simply because the study was too small (and thus lacked statistical power) or because some imprecision or limited sensitivity of the parameters precluded a more definitive observation. These limitations may be aggravated when toxicology is influenced by vested interests. Because current toxicology overlooks the important goal of achieving a better characterization of uncertainties and their implications, research approaches should be revised and strengthened to counteract the innate ideological biases, thereby supporting our confidence in using toxicology as a main source of documentation and in using the Precautionary Principle as a decision procedure in the public policy arena.

Keywords: Precaution, Public Health, Toxicology, Research

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The need for toxicology research

Empirical studies in toxicology aim at deciphering causal relationships in regard to chemically-related human diseases. To support disease prevention and health promotion, the experimental and epidemiological research must provide documentation that can lead to informed decisions on public policy. Due to the complexity of exposures to environmental chemicals and the barriers against controlling chemical releases in society, authorities need guidance from toxicology to decide upon efficient regulatory strategies to protect human health.

The need for toxicology research is indicated by the substantial part of the total burden of disease in industrialized countries that has been attributed to environmental factors. The bulk of this amount is affecting children and vulnerable groups, such as the poor and women in reproductive age [1]. A recent report from the U.S. National Research Council estimated that a large portion of developmental disorders in children is caused by environmental factors [2]. Lead poisoning appears to be the most important environmental risk factor in regard to children's health [3]. However, all estimates of this kind are approximate and based on expert judgment from information on a small number of individual hazards that represent only a small portion of the total exposure burden. Apart from our dependence upon a healthy global ecology, environmental disease causation is highly important from a public health standpoint, but its true impact is bound to be seriously underestimated owing to the lack of documentation.

At the same time, scientific information on the health effects of most industrial chemicals is either limited or nonexistent [4]: Nearly 3 out of 4 (71%) of the sampled high-priority chemicals did not meet the minimum data requirements for health hazard screening set by the

Organization for Economic Cooperation and Development (OECD) chemicals program. Of the nearly 3000 high production volume (HPV) chemicals, which are made or imported to the United States at more than 1 million lbs/year, only 7% possessed a complete set of publicly available screening data on their toxicity [5]. This review also found that 43% of HPV chemicals had no testing data on basic toxicity. Among 491 chemicals used by children and families in consumer products, only 25% had full screening data [5]. Furthermore, not all potential adverse effects are included in the tests required by the authorities. For example, neurotoxicity tests (in chicken) are normally required only for cholinesterase inhibiting pesticides [6]. Thus, even for those chemicals that have been tested, limited information exists on how those substances can influence human health at environmental levels of exposure.

About 70% of the chemicals marketed in the European Union after 1981, and for which detailed testing was required, are considered hazardous and must be labeled accordingly and restricted in regard to usage. Similar requirements are enforced for only a small percentage of chemicals already marketed before that time, mostly because a hazard assessment is impossible due to the lack of toxicology data. This unfortunate lack of information is mainly due to the inappropriate allocation of responsibilities, where regulatory authorities are usually responsible for the toxicity assessment instead of the enterprises that produce, import, or use the substances [7].

Research into the chemical causation of disease is fraught with difficulties. The most obvious etiologies have already been found, including causes of acute poisonings. A far more difficult subject area remains to be disentangled in regard to the impact of mixed and irregular

exposures, chemical interactions, and genetic predisposition. Most outcomes are likely to be non-specific and delayed, and many research designs will therefore lead to an underestimation of the true magnitude of the health hazards.

Too often, toxicology research has hailed the safe strategy of examining known toxicants and refrained from exploring less predictable and poorly known chemicals. As a result, the majority of published papers in toxicology and environmental health journals deal with a limited, rather stable list of pollutants. For example, by December 2003, the U.S. National Library of Medicine listed over 15,000 publications in scientific journals about lead. In contrast, less than 50 papers dealt with newer toxicology problems, such as perfluorooctane sulfonates.

Even in regard to toxicants identified early on, efforts to control the hazard and protect human health were often substantially delayed, with the result of unnecessary human suffering and environmental degradation [8]. The hiatus between toxicology and public health is also apparent from the historic courses of exposure limits. In regard to inorganic lead, a critical review of the toxicology data led the Center for Disease Control (CDC), in 1960, to decide on an action level for the blood-lead concentration in children at 600 µg/liter (2.9 µmol/liter). As evidence on lead toxicity accumulated, the limit was repeatedly lowered; 30 years later, the action level had been decreased to 100 µg/liter (0.5 µmol/liter) [9]. Today, many public-health professionals support a reduction of the action level by 50% [10]. In hindsight at least, enough information was available much earlier to trigger the stricter actions, but the adverse health impact was ignored for several decades because of lack of definitive evidence. Although scientific documentation in this

case was belatedly translated into prevention, most environmental toxicants are far less understood, and human exposures are therefore virtually unregulated.

New information will be forthcoming more rapidly than in the past, since the OECD is coordinating an international effort to screen the HPV chemicals, and further efforts have now been proposed. Among substances known to be used in Europe before 1981, about 30,000 are marketed in volumes above 1 ton per year. The European Commission has presented draft principles for obtaining basic toxicological information on those of the chemicals about which little is known [11]. However, U.S. authorities have protested against the proposal and threaten to contest this requirement within the World Trade Organization [12]. With time, additional data will somehow emerge, though only slowly and mainly focusing on limited aspects of so-called priority chemicals. Many uncertainties will therefore prevail.

Because anthropogenic changes in the environment are occurring at a greater pace, our improved understanding of the world is lagging further behind in determining the risks to human health and the environment. New knowledge will not eliminate uncertainty as a permanent concern. Gaps in critical knowledge will continue to complicate decisions on efforts to reduce or eliminate chemically-associated diseases.

Limits of science for decision-making

As a scientific discipline, toxicology must obey the same rules that apply to the biomedical field in general. A main challenge is to examine variability and to distinguish individual sources of systematic variation from those that are random and thereby part of what we may in general refer

to as incertitude [13]. The simplest dimension of incertitude is so-called risk, which encompasses variability owing to factors such as imprecision and sampling errors in the database. Uncertainty (in the narrow sense of the word) involves incomplete knowledge on the type of adverse effect, the particular aspect of the exposure that may be harmful, the dose-response model, the impact of combined exposures, and similar considerations that cannot be settled from current information. Ignorance is considered when even less information is available, but may still be potentially remedied by further research. The final aspect is indeterminacy, where the problem shows dependence on multiple variables or chaotic properties that defy attempts to predict the outcome [14].

Even if variability originates from a single source, such as genetic heterogeneities or age, it may be substantial. A recent study evaluating differences in human response to airborne particles found that the most sensitive members of a population respond to doses 150 to 450-fold lower than median (50th percentile) responders [15]. Factors that contribute to these differences include variations in breathing rates, deposition and elimination of air particles from the respiratory tract, and differences in lung response to the chemicals found in the air.

In its quest to extract new knowledge from empirical observations, science has important limitations. As stated by the British biostatistician, Austin Bradford Hill [16], "All scientific work is incomplete... All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us the freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at the given time." Indeed, the responsibility of the toxicology researcher is that the science is properly translated into public policy that may protect

human health. Still, researchers sometimes mistake the validity of their own conclusions for meticulousness in identifying presumed violations of the causal "criteria" once presented by Sir Austin.

Short-comings of toxicology research

Toxicology must address uncertainty in an efficient and responsible way, often balancing on a knife's edge when focusing on manageable scenarios or models, without sacrificing the external validity by reducing the object to narrow issues that bear little resemblance to the real world. Despite the remarkable progress in toxicology and the indisputable role of this scientific field in society, current approaches in toxicological research appear non-precautionary and therefore miss important opportunities to provide guidance for prevention.

Most toxicology research focuses on simplified model systems and the effects of purified single hazards, one at a time. When a toxic response has been encountered, the need for replication to obtain confirmatory evidence tends to penalize false positives more than false negatives. Even a confirmed toxic effect may have little implication for the real-world situation, where people are exposed to low-dose mixtures of hundreds of different chemicals. The toxicity of these mixtures is not known, and is rarely being investigated. However, two recent studies reported results of dosing laboratory animals with mixtures of organochlorine chemicals, metals, and pesticides, each applied in regulatory "safe" doses, but with resulting adverse effects that could not have been predicted from current knowledge [17,18].

Insufficient attention is paid to sources of variability and uncertainty, including individual susceptibility, impacts of mixed and variable exposures, susceptible life-stages, and vulnerable communities. Another important source of uncertainty is measurement error that results in misclassification, especially in regard to exposure assessment. Standard statistical analysis assumes that the exposure is measured without error, and imprecisions will usually result in an underestimation of the dose-effect relationship [19]. In testing whether an effect could be considered a possible result of natural variability, a 5% limit for “statistical significance” is usually applied, even though it may rule out many findings of causal associations, simply because the study was too small (and thus lacked statistical power) or because some imprecision or limited sensitivity of the parameters precluded a more definitive observation.

Lack of scientific data, or lack of a statistically significant association, is of course not the same as proof of harm or the opposite. Any conclusion about safety is unfounded, but the absence of evidence is often assumed to mean evidence of absence of a hazard. This issue is particularly relevant in regard to widely occurring low-dose exposures, which may span a complete lifetime (‘from womb to tomb’). The limited guidance from current toxicology is related to the study designs, required by food and drug regulations that do not require testing of low doses, and especially not lifetime exposures. As a complicating factor, some chemicals produce different or even opposite effects at high and low doses — a phenomenon called biphasic dose response, with endocrine disruptors as clear examples [20].

Misuse of toxicology research

Clinical medicine has come to rely upon ‘evidence-based’ recommendations, which are meant to serve as scientifically-based rules to protect against error. This emphasis on documentation is appropriate for drug therapy, diagnostic methods, and surgical procedures, and it has served health care services well. However, in extending evidence-based decisions to toxicology, the argument is often turned the other way around: prevention must be justified by evidence. Chemicals are therefore regarded innocent and inert, unless proven otherwise. This assumption is of course not justified, and past experience has amply documented its serious consequences in regard to asbestos, benzene, and polychlorinated biphenyls, to name a few examples [8].

During recent years, scientific ambitions of understanding the molecular aspects of toxicology have become a stumbling block when toxicological mechanisms of action were demanded as a prerequisite for risk assessment, especially for carcinogens. Di(2-ethylhexyl)phthalate (DEHP) was thought to be a carcinogen, and an intense research effort was therefore launched to identify reasons why its carcinogenicity in rodents should not apply to humans [21]. The International Agency for Research on Cancer responded to the doubt raised by downgrading the classification of this substance from “possibly carcinogenic” to “not classifiable”.

The monotone dose-response curve has come under attack by observations that suggested the possible existence of so-called hormesis at low dose [22]. Although such dose-associations may well occur in certain cases (e.g., in regard to essential nutrients), the scattered evidence by no means justifies any generalization that would suggest that low doses of toxic compounds are advantageous to health. Likewise, pragmatic application of linearized dose-response relationships

has been challenged, because other models led to widely differing risk assessments [23]. In addition, the use of uncertainty factors has been challenged as lacking scientific justification [24].

Within epidemiology, an international call for guidelines on ‘Good Epidemiological Practice’ first appeared to serve a useful educational purpose. It later backfired when strict interpretation of the epidemiological rules was applied by industry groups to discredit epidemiological findings that were regarded unwelcome (e.g., adverse effects of environmental tobacco smoke) [25]. In this atmosphere, scientific rigor became misunderstood as the unrealistic need to conduct controlled experiments with statistically definite conclusions. Inconclusive studies were labeled ‘negative’ and were thought to represent ‘no risk’ rather than ‘no information’. These controversies had the overall effect of blurring the rules of evidence, including the hierarchy of knowledge, evidence, documentation, and individual results.

Selective publication of studies with statistically significant results is widely recognized [26], and outcome reporting bias has also been documented [27]. Although such bias could potentially cause a tendency of favoring false positive results, studies of pharmaceuticals have shown that toxicity or side effects tend to be disregarded in studies or reviews sponsored by industries with a vested interest. Chemical industries also have a well documented record in misrepresenting, hiding, or falsifying scientific evidence [28].

Documents obtained in connection with recent law suits have revealed the strategies of one of the major industrial contributors to controversies in toxicology. A proposal for a public relations strategy from the Brown & Williamson tobacco company acknowledges that ‘doubt is our product since it is the best means of competing with the “body of fact” that exists in the mind

of the general public'. In addition, 'it is also the means of establishing a controversy' [29]. These statements provide insight into the reasoning of a major vested interest. Because skepticism is a premise in science, this marketing strategy found a receptive audience among toxicology professionals, some of whom were likely rewarded with research grants.

From a wealth of evidence, Krimsky [30] has recently suggested that commercially sponsored research needs to be separated from academic research at public institutions and universities. This proposal has been seconded by Rennie, Deputy Editor of the *Journal of the American Medical Association (JAMA)* [31], who has said that "dependence on company money 'corrupts and crows' university researchers," that, to thwart publication of unfavorable research reports, "pharmaceutical firms have threatened researchers, interrupted trials, and blocked publications," and that, to create an impression of a robust body of research, "firms have promoted multiple publication of slender research results, sometimes shuffling the sequence of the researchers' names to disguise the repetition." One journal in the field, *Regulatory Toxicology and Pharmacology*, has attracted attention because of its obvious bias in publishing viewpoints supporting particular industry positions disguised as scientific papers [32].

Precautionary toxicology

Toxicology has failed the purpose of science in society by striving to reach only the limited goals of solving simplified riddles and in recognizing, rather than exploring uncertainty. By ignoring the larger perspectives of chemical causation of disease, it has failed its responsibility to contribute to the foundation of disease prevention.

The precautionary principle (PP) has been launched as an appropriate remedy to counterbalance the emphasis of vested interest groups on scientific doubt and the resulting demands for deferring preventive actions [33,34]. Simply stated, the PP says that, in situations of potentially serious or irreversible threats to health or to the environment, the need to act to reduce potential hazards before there is strong proof of harm, should take into account likely costs and benefits of action and inaction. It was introduced as the ‘Vorsorgeprinzip’ in social context in Germany during the 1930s, then formally extended to environmental policy during about 1970 as a planning instrument. The modern PP was born and included in the first convention on protection of the North Sea in 1984 and is now part of the EU treaty.

As stated in the European Environment Agency document on ‘Late lessons of early warnings’, uncertainty need to be incorporated in technology appraisal and public policymaking, and the gaps in scientific evidence must be identified so that efforts may be targeted at reducing them [8]. The key element of the PP is the justification for acting in the face of uncertain knowledge about risks from environmental exposures. Appropriate public health action should be taken in response to limited, but plausible and credible, evidence of likely and substantial harm. The PP is thereby aimed at avoiding possible future harm associated with suspected, but not conclusive, environmental risks. The burden of proof is shifted from demonstrating the presence of risk toward demonstrating the absence of risk. The PP is not a prescription for banning the use of industrial chemicals, but it requires that alternative options be evaluated to minimize the costs of detrimental surprises and maximize the benefits of innovation.

Toxicology needs to find its future place in this perspective, and research approaches must be developed and strengthened to counteract the innate ideological biases. In supporting decisions based on the PP, documentation must be acknowledged as provisional and dynamic, and a dynamic interface must be nurtured between science and decision-making, with stakeholder participation. Because public-policy decisions may require new targeted research, monitoring and surveillance, future toxicology research must support the entire process from hazard identification to intervention evaluation.

In regard to toxicology research planning, analysis, and reporting, some revision would seem necessary. Proximate and simplistic risks and unrestrained replication should no longer be favored. Risk assessment must become less reductionist and less focused on obtaining complete information on all aspects of individual hazards. Statistical acceptance of the null hypothesis should never be interpreted as proof of safety. Rather, calculation of confidence limits should be incorporated and the full span of uncertainties should be determined to allow appropriate estimation of the possible extent of a hazard.

Given that decisions will involve stakeholders, risk perception should receive increased attention as a crucial aspect that is not dependent on a formalized scheme of evaluation. Risk assessment can never become completely objective, and the European Commission [35] has therefore initiated discussions on how qualitative risk aspects, such as ethical values, animal welfare, quality of life issues, socioeconomic considerations, and sustainability can be incorporated into the process. This important initiative closely follows the recommendations by a US committee [36]. Toxicology needs to adapt to these developments, as well.

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Table 1. Scientific features that may bias toxicology toward missing a true association (false negative) (revised from [34])

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|---|
| <i>Toxicological studies in general</i> |
| Low statistical power |
| Use of 5 % probability level |
| Use of 20% probability level to minimize risk of type II error |
| Pressures against false alarm |
| <i>Epidemiological studies of toxicants:</i> |
| Inappropriate control group |
| Exposure misclassification |
| Inadequate follow-up of exposed subjects (cases lost to follow-up, follow-up too short) |
| <i>Experimental toxicology:</i> |
| Exposure to single substances, one at the time |
| Limited number of dose levels |
| Exposure duration less than lifetime |
| Standard effect measures |
| Inbred strains to limit genetic variability |
